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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MCINTOSH III, TRAVISS C

ART UNIT	PAPER NUMBER
1623	6

DATE MAILED: 09/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/972,854	BESSODES ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Acknowledgement is made to the preliminary amendment filed November 12, 2002 in which applicant cancelled claims 1-16 and 30-38. Upon review of these claims, and of the restriction requirement set forth in the Office Action mailed June 2, 2003, the examiner has withdrawn the restriction requirement and will examine all currently remaining claims, 17-29. The species requirement has been maintained as applicant's arguments were not found to be convincing, and acknowledgement is made to the election of species wherein the hydrophilic substituent elected is a polyalkylene glycol.

Claim Objections

Claim 26 is objected to because of the following informalities: the sentence ends in a comma rather than a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is confusing wherein the claim is drawn to "a composition comprising at least one acid-sensitive compound, or a salt thereof, comprising a cyclic ortho-ester and at least one hydrophilic substituent chosen from...". Does applicant intend the composition to comprise: 1)

an acid sensitive compound comprising a cyclic ortho-ester and a hydrophilic substituent; or 1) an acid sensitive compound comprising a cyclic ortho-ester, and 2) a hydrophilic substituent? That is, does the composition comprise:

1) an acid sensitive compound comprising,

a) the ortho-ester, and

b) a hydrophilic substituent,

or does the composition comprise:

1) an acid sensitive compound comprising,

a) the ortho-ester, and

2) a hydrophilic substituent.

Clarity is respectfully requested. It is noted that the examiner has interpreted the claims as a composition comprising:

1) an acid sensitive compound comprising,

a) the ortho-ester, and

b) a hydrophilic substituent.

Since the composition as interpreted comprises only one active agent, the claim is indefinite. A composition must contain more than 1 agent, otherwise what is claimed is not a composition, but a compound. Adding an additional additive to the composition will obviate this rejection (carrier, diluent, excipient, etc.).

Claims 17 and 18 include the limitation of "**substituted**" when referring to "an amino group that is optionally substituted". In the absence of the identity of moieties which are intended to be substituted, thus modifying an art recognized chemical core, described structurally or by

chemical name, the identity of "substituted" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" are not described sufficiently to distinctly point out that which applicant intends as the invention.

Claim 18 is drawn to a composition optionally comprising "a steroid derivative". In the absence of the identity of moieties intended to modify an art recognized chemical core, described structurally or by chemical name, the identity of a derivative would be difficult to ascertain. In the absence of said moieties, the claims containing the term "derivative" are not described particularly sufficiently to distinctly point out that which applicant intends as the invention.

Claim 19 is indefinite wherein the claim is drawn to the composition of claim 18 and further comprising a biologically active substance. The examiner is unclear as to what is intended by a biologically active substance and one of ordinary skill in the art would not be able to ascertain the scope which applicants are seeking protection for by this recitation.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

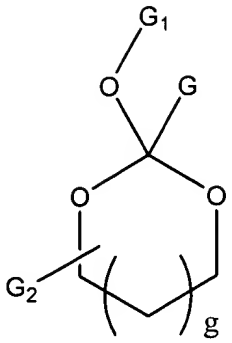
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

> Determining the scope and contents of the prior art.
> Ascertaining the differences between the prior art and the claims at issue.
> Resolving the level of ordinary skill in the pertinent art.
> Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Nantz et al. (US Patent 6,200,599 B1) and Rodrigues et al. ("Acid Sensitive Polyethylene Glycol Conjugates of Doxorubicin: Preparation, In Vitro Efficacy and Intracellular Distribution", Bioorganic and Medicinal Chemistry, vol. 7, 1999, pp. 2517-2524).

Claim 17 of the instant application is drawn to a composition comprising an acid-sensitive compound which comprises a cyclic ortho-ester and a hydrophilic substituent (a polyalkylene glycol). Claim 18 is drawn to a composition comprising the structure:

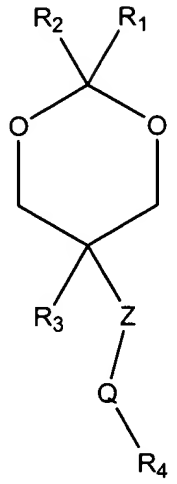


wherein g is 0-4;

G is H or 1-6C alkyl, or aryl;

and G_1 and G_2 are selected from one being a polyalkylene glycol and the other being a single or double chain alkyl, a steroid, a hydrophobic dendrimers, or a covalent conjugate of these. Claim 19 provides the limitation that the composition additionally comprises a biologically active agent. Claim 20 limits the biologically active substance to a multitude of agents. Claim 21 provides that the composition additionally comprises an adjuvant. Claim 21 provides that the adjuvant is a neutral lipid. Claims 23-27 limit the lipid to various lipids including optionally dioleoylphosphatidylethanolamine (DOPE). Claims 28 and 29 provide the limitation that the composition additionally comprise a vehicle for injectable formulations or topical formulations (to the skin or mucous membranes).

Nantz et al. teach of ortho-ester lipids which upon a certain pH, undergo hydrolysis with the concomitant or subsequent head group cleavage. The structural representation of the ortho-ester taught is represented by the following structure:



wherein the ring can be expanded with from 1-4 additional CH_2 moieties;

R_1 is a functional group;

R_2 is a functional group;

R_3 is a functional group;

Z is a functional group (a linker);

Q is a functional group (a cleavable group); and,

R_4 is a nitrogen-containing head group (column 2, line 45- column 3, line 19). The variable functional groups of the compound include, an ortho-ester function, a hydrophobic domain, a linker, a cleavable group, and a hydrophilic domain or a nitrogen head group (column 6, lines 30-34). R_1 is taught to be an alkyl chain which can be a short chain or a long chain (column 7, lines 16-18). R_2 is taught to be optionally an alkoxy group and R_3 is optionally H (column 6, lines 58-59). The compound of exploits the susceptibility of the ortho ester functional group toward acid induced hydrolysis. Moreover, the putative mechanism of action for the ortho ester lipids involves structural reorganization of the lipids beyond their protonation. Acidification of ortho ester lipids results in lipid (and liposome) structural changes i.e., ortho ester conversion to

an ester with headgroup cleavage and liposome disassembly. Thus, the compounds of Nantz et al. are advantageously incorporated into liposome formulations. Nantz et al. teach the liposomes to comprise the compound itself, or additionally to comprise a helper lipid, preferably non-ionic or uncharged lipids such as DOPE or cholesterol. (column 9, lines 15-31). What is not taught by Nantz et al is to utilize a polyalkylene glycol as the hydrophilic group nor to add a vehicle for topical and/or injectable formulations.

Rodrigues et al. teach of polyethylene glycol compounds which are non-ionic, water soluble synthetic polymers which a potential drug carriers due to their synthetic diversity and recognized biocompatibility (page 2517, 1st paragraph). These conjugates are designed to increase the water solubility of the drug while slowly releasing the parent compound through hydrolysis of the chemical link between the drug and the polymer backbone.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polyethylene glycol moiety which is attached to the active drug as the hydrophilic group of Nantz et al. because Rodrigues et al. teaches that the acid-sensitive PEG conjugates allow the PEG-drug complex to be released in the acid environment of endosomes and/or lysosomes after cellular uptake of the conjugate by endocytosis. The ortho-ester complex of Nantz et al. is taught to undergo acid-induced hydrolysis to their corresponding esters, and further fragmentation of the resultant ester breaks it into its constituent parts. Ortho ester conversion to its ester, with the concomitant or subsequent head group cleavage results in liposome disassembly. The pH-induced hydrolysis of the ortho ester moiety promotes liposome disassembly by altering the lipid molecular structure or by altering its amphiphilicity (by loss of polar head groups). One would be motivated to use the polyethylene glycol as the hydrophilic

head group as Rodrigues et al. teaches that a PEG-drug complex is also a complex which requires an acid induced drug releasing mechanism thus providing a liposome complex which would break-down in a acidic pH thus releasing its PEG-drug complex, which additionally breaks down in the acidic environment, ultimately releasing its active agent.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh
September 10, 2003